Abstract

Introduction and Goal

Leishmaniasis is widespread in many parts of the world, with the prevalence in more than 98 countries. According to the World Health Organization reports, the annual incidence of the disease is 2 million. There is no vaccine for this disease and there are few effective drugs to treat it. Drug resistance to the disease is increasing. Based on the clinical manifestations, they are classified into three general categories: visceral leishmaniasis, cutaneous leishmaniasis, and mucosal leishmaniasis. Iran is one of the endemic areas of Leishmania. During the past decade, numerous *in vitro* and *in vivo* studies have been performed on dihydropyrimidine derivatives and a number of heteroaryl containing compounds have been demonstrated to possess anti-leishmanial effects.

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Materials and Methods

Acyclic enamino amide intermediate compounds were prepared via reaction of primary aromatic amines with dioxin and xylene under reflux. After formation of the intermediates (beta-keto-amides), the final derivatives were synthesized using 4-methoxybenzylamine and isopropyl alcohol. The mechanism of synthesis is initiated by reverse Diles-Alder reaction of the dioxin ring and subsequent capture of the acetyl ketene intermediate by amines. Also for the synthesis of cyclic dihydropyrimidinenone/thione compounds, the previously obtained beta-keto amide intermediates were reacted with urea/thiourea, corresponding aldehydes, HCl or cobalt sulfate *II* in ethanol. Structural characterization of the synthesized compounds were performed using TLC, melting point determination, infrared spectrometry (IR), mass spectrometry (MS) and proton-core magnetic resonance (H-NMR) technique. Subsequently, the cytotoxicity assessment of thiazole salt (MTT) was evaluated on Leishmania major promastigote parasites.

Results

Based on the results of NMR, IR and MS identification tests, all the synthesized structures were confirmed. Anti-leishmanial effects were evaluated on Leishmania major species and compound **A10** (4-(3-chlorophenyl)-6-methyl-*N*-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide) with IC_{50} 52.67 µg/ml exhibited the best anti-leishmanial effect (more than standard drug glucantim with IC_{50} 71.01 µg/ml).

Discussion and conclusion

Based on the results, 6-methyl-3,4-dihydropyrimidine-2-thion derivatives were better anti-leishmanial agents within assessed compounds. Highr antileishmanial effects of the mentioned derivatives may be attributed majorly to 1) substitution of 2-carbonyl with 2-thiocarbonyl moiety and 2) substitution of 4-(*N*-benzyl) with of 4-(*N*-phenyl) substituent. Moreover; structure-biological relationship showed that the isoxazole and benzothiazole rings attached to the amine core of the acyclic enamino amides reinforced anti-leishmanial activity with regard to thiazole.

Key words

Leishmaniasis, Synthesis Enamino amide, Dihydropyrimidinone, MTT